Cerebral Vasospasm affects Arterial Critical Closing Pressure

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Abstract

The effect of cerebral vasospasm (CVS) following aneurysmal subarachnoid hemorrhage (SAH) on critical closing pressure (CrCP) has not been fully delineated. Using cerebral impedance methodology, we sought to assess the behavior of CrCP during CVS. As CrCP expresses the sum of intracranial pressure (ICP) and vascular wall tension, we also explored its role in reflecting changes in vascular tone occurring in small vessels distal to spasm.

This retrospective analysis was performed using recordings from 52 patients, diagnosed with CVS through transcranial Doppler measurements. CrCP was calculated non-invasively using arterial blood pressure and blood flow velocity. Outcome was assessed at both discharge and 3 months after ictus with the Glasgow Outcome Scale.

The onset of CVS caused significant decreases in CrCP ($p=0.025$), without any observed significant changes in ICP ($p=0.134$). Vasospasm induced asymmetry, with CrCP ipsilateral to CVS becoming significantly lower than contralateral ($p=0.025$). Unfavorable outcomes were associated with a significantly lower CrCP after the onset of CVS (discharge: $p=0.014$; 3 months post SAH: $p=0.020$).

CrCP is reduced in the presence of CVS in both temporal and spatial assessments. As ICP remained unchanged during CVS, reduced CrCP most probably reflects a lower wall tension in dilated small vessels distal to spasm.

Key words: critical closing pressure, subarachnoid hemorrhage, vasospasm, wall tension

Introduction

Cerebral vasospasm (CVS) is one of the most deleterious complications following subarachnoid hemorrhage (SAH)[1–3], being thought to disturb cerebral haemodynamics, leading often to hypoperfusion[3–5] and contributing to delayed cerebral ischemia (DCI)[6–8]. However, the stenosis of the spastic artery alone cannot fully explain the subsequent development of DCI, as not all patients with CVS, detected either radiologically or with transcranial Doppler (TCD), develop DCI[8–10].

For this reason, assessment of changes in the cerebral microvasculature distal to spastic vessels may be important. However, previous studies have yielded conflicting results. Positron emission tomography and radioisotope studies have reported findings of maximal vasodilatation[11,12] and an impaired vasoreactivity distal to spastic segments[13,14], whereas another experimental study reported narrowing of intraparenchymal arterioles post SAH[15]. Moreover, both TCD and Near Infrared Spectroscopy techniques have demonstrated that an early onset of dysautoregulation before vasospasm correlates with the occurrence of DCI but not with a worse outcome[16], unless autoregulatory failure spreads to both hemispheres.[17] This may further complicate our understanding of the microvasculature's role in SAH.

A parameter that could aid in this situation is critical closing pressure (CrCP), which estimates the theoretical lowest value of arterial blood pressure (ABP) that is adequate for maintaining cerebral blood flow[18]. Any value of ABP below this threshold will result in a collapse of small vessels, leading to cessation of blood flow. CrCP has been modelled as the sum of intracranial pressure (ICP) and vascular wall tension (WT) of small vessels[19]. Therefore, observation of how CrCP and WT vary can provide an insight into the dynamics of cerebral resistive vessels and its behavior in pathological states like CVS.

The use of CrCP in clinical practice has been restricted by methodological drawbacks, namely due to presence of difficult to interpret negative CrCP values in conditions with increased cerebral blood flow velocity[20–23], including CVS[24]. We have recently described a method for estimating CrCP based on cerebrovascular impedance[25,26], which has demonstrated a good correlation with traditional methods in many clinical conditions[26,27], without yielding negative values.

The primary aim of our study was to describe the behavior of CrCP during CVS. First, because the state of the microvasculature in SAH is unclear, and with CrCP being related to vasomotor tone, we examined whether any changes in CrCP presented during CVS could be indicative of changes in the microvascular wall tension distal to spasm. Secondarily, we explored the relationship of CrCP with autoregulation and how this relationship becomes affected with CVS. Finally, we also explored the existence of any association of CrCP and outcome following SAH.

Methods

Patients

We retrospectively analyzed prospectively collected data from a group of 98 aneurysmal SAH patients admitted to the Neurocritical Care Unit of Addenbrooke's Hospital, Cambridge (June 2010-January 2012)[16,28]. Approval of the study was given by the Addenbrooke's Research Ethics Committee. Patients gave written informed approval for the study or in case they were incapacitated, the written consent was signed from next-of-kin. The guidelines governing the prospective study on which this retrospective analysis is based on have been reported previously by Budohoski et al[16], where the cohort was assessed from the aspect of early changes in cerebral autoregulation.

Bilateral TCD measurements at the temporal window (depth of 40-60 mm) were used to identify CVS in a total of 52 patients [median age: 52 years (interquartile range 45-60); females/males: 36/16] who had a mean blood flow velocity (FV) in the middle cerebral artery (MCA) exceeding 120 cm/s, with a concomitant Lindegaard Ratio (LR) of above 3.0 on TCD[29]. Overall patient characteristics are presented on Table 1 (Section A). The median onset of CVS was 6 days post SAH. Cerebral perfusion was optimized with the use of hypertension, hypervolemia, and hemodilution as part of the triple-H therapy in patients who developed DCI (31/52 of CVS patients)[16,30]. The Glasgow Outcome Scale (GOS) was used for assessing outcome at both discharge from hospital and 3 months post SAH.

Monitoring and Data Analysis

Monitoring periods included recordings of ABP, ICP and bilateral FV, performed every 1-2 days[16]. ABP was measured either from the radial artery using a pressure monitoring kit (Baxter Healthcare, Deerfield, IL, USA), or non-invasively with a Finapres 2300 finger plethysmograph (Ohmeda, Amsterdam, The Netherlands) zeroed at the heart level in all patients. Patients were supine with the head of the bed raised 30-45 degrees. Patients requiring ventriculostomy for hydrocephalus (N=21) had an external ventricular drain (EVD), which was used for drainage of cerebrospinal fluid when open and for ICP measurements when closed. The external drainage was closed during the TCD monitoring period, preventing possible interference of high cerebrospinal compliance (open EVD) with cerebral hemodynamics. Out of these 21 patients, 14 had a full set of measurements both before and during CVS that were used for analysis of change in ICP during CVS. Doppler monitoring of FV was performed bilaterally at MCAs, with the use of a DopplerBox (DWL Compumedics, Singen, Germany) and a head positioning device (Lam Rack, DWL Compumedics) via the temporal window at a depth of 45-60 mm. The raw data signals were recorded at sampling

frequency of 200 Hz using ICM+ software (Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus/). Mean values of signals were calculated in ICM+ by averaging values in a 10-second time window and then secondarily averaging them over whole monitoring time (20-40 min). Heart rate was calculated using spectral position of the peak associated with the first harmonic of ABP.

Cerebral autoregulation was assessed with a TCD-derived autoregulation index, Sxa, calculated as a moving correlation coefficient between ABP and systolic FV, from a 300-second window with averaging every 10 seconds[16].

Estimation of Critical Closing Pressure

CrCP was estimated with the impedance methodology[25,26], using a non-invasive version requiring signals of ABP and TCD FV[31]:

$$CrCP = ABP \cdot [1 - \frac{1}{\sqrt{(CVR \cdot Ca \cdot HR \cdot 2\pi)^2 + 1}}]$$

CVR stands for cerebrovascular resistance with Ca representing arterial compliance of the cerebral bed. Calculation of CVR and Ca can be perfomed with algorithms based on measurements of FV and ABP, presented in previous studies[32,33]. HR represents heart rate (beats/s).

Please see the Appendix for further details regarding non-invasive CrCP methodology.

Statistical analysis

The IBM SPSS Statistics 20 package (Armonk, NY, USA) was used for the statistical analysis. The Shapiro–Wilk test was used to confirm normal distribution of the samples.

Results are presented in a mean value ± standard deviation (SD) format. Bivariate correlations were used, with R being the Pearson correlation coefficient. The level of significance (p-value) was set at 0.05.

For analysis of CrCP in cases of unilateral CVS, the TCD recordings from the side ipsilateral to CVS were used, whereas when bilateral CVS was present, the analysis included averaging of both sides.

Temporal and spatial comparisons were used to assess how CrCP was affected by the presence of CVS, performed with paired samples T-tests. In temporal comparison, the cohort of CVS patients was dichotomized in time, with comparison of averaged periods before and during CVS, based on the TCD onset of CVS for each patient. Spatial analysis included bilateral comparisons (ipsilateral-contralateral to CVS). Both temporal and spatial comparisons were made using data of patients with recordings both before and during CVS (37 patients out of the total 52; Figure 1).

Autoregulation analysis included averaged periods of calculated autoregulatory index Sxa, before and during CVS, with the relationship to CrCP being explored through correlation to the respective averaged periods of CrCP.

Outcome analysis consisted of comparisons between favorable (GOS: good recovery, moderate disability) vs unfavorable (GOS: severe disability, vegetative state, death) outcomes, for the patients who had recordings both before and during CVS (N=37). Comparisons included then averaged recordings of CrCP and FV for several days both before and after the CVS onset. The outcome scores were collected at discharge and at 3 months after injury. Binary logistic regression models were used for analysing the association of CrCP to outcome. Section B of Table 1 presents a comparison between patients of favorable

and unfavorable outcomes, with the latter presenting a significantly worse WFNS score and a higher percentage of occurrences of hydrocephalus and DCI.

The rest of SAH cohort that did not develop CVS (46 out of 98 patients) was used as a control group, where CrCP was averaged for the whole monitoring period.

Results

Effects of vasospasm on critical closing pressure

Mean values of measured parameters and CrCP before and during CVS are presented in Table 2. CrCP became significantly lower during CVS, decreasing by 14.7% after the onset of CVS ($p=0.025$). FV was significantly increased during CVS ($p<0.001$), as was ABP ($p<0.001$).

ICP did not significantly change during CVS, even though a tendency to decrease was observed after the onset of CVS (before CVS: 13.55 ± 4.04 mm Hg; after onset of CVS: 11.04 ± 5.78 mm Hg; $p=0.134$, $N=14$). Changes in ICP were not correlated to changes in CrCP from before to during vasospasm (absolute changes; $p=0.379$, $N=14$).

Changes in CrCP observed in time after SAH were not associated with changes in FV, as the absolute difference of CrCP before and during CVS was not correlated with the respective absolute difference of FV ($R=-0.227$; $p=0.177$). The independence of CrCP and FV was further confirmed with an overall absence of correlation between them during CVS ($p=0.148$).

No significant interhemispheric difference could be found in either CrCP or FV before the onset of CVS ($p=0.394$ and $p=0.143$ respectively). However, the presence of CVS reduced CrCP in both hemispheres and induced asymmetry, with CrCP ipsilateral to CVS becoming

significantly lower than contralateral CrCP during to CVS (p=0.025; Figure 2). Ipsilateral FV was significantly higher than contralateral FV during CVS (154.13 ± 44.94 vs 104.45 ± 40.58 cm/s; p<0.001).

Interhemispheric changes in CrCP were not correlated to changes in FV during CVS (R=0.056; p=0.763). The interhemispheric asymmetry of CrCP was not constant across the days post SAH, with the biggest differences being on days 11 and 12 (Table 3).

Comparison of CrCP values of CVS patients to a control group, consisting of the rest 46 SAH patients (out of a total 98) that did not develop CVS, demonstrated a significantly lower CrCP in CVS cases (CrCP after the onset of vasospasm in CVS patients: 40.70 ± 16.72 mm Hg; CrCP in SAH patients without no presence of vasospasm: 34.67 ± 9.77 mm Hg; p=0.015). No significant difference could be found between the control SAH group and the averaged period before the presence of vasospasm for the CVS patients (p=0.659).

Autoregulation

Sxa and CrCP were inversely correlated before CVS (R=-0.329; p=0.043). Autoregulation presented signs of impairment during CVS, as shown by a significantly increased Sxa (from 0.14 ± 0.18 to 0.22 ± 0.15; p=0.023). During CVS, there was no correlation between Sxa and CrCP (R=0.122; p=0.471).

Outcome

Compared to patients with favorable outcome (N=29), unfavorable cases (N=8) had a significantly lower CrCP during the CVS period, with outcome assessed both at discharge

(p=0.014, Figure 3A) and at 3 months post SAH (p=0.020, Figure 3B). No association was found between CrCP before CVS onset and outcome (p>0.05 for all).

Adjusting for FV during CVS, binary logistic analysis (with independent parameters CrCP and FV) indicated a lower CrCP to remain significantly and independently to FV associated with unfavorable outcome (Table 4).

Discussion

Overall, during cerebral vasospasm we observe significant decrease in CrCP. This could be seen both in temporal assessment where the onset of CVS resulted in a decrement of CrCP, and in spatial investigation, where CVS caused an interhemispheric CrCP difference, with a lower CrCP ipsilateral to spasm. This could be also seen when comparing to a control group of SAH patients without presence of CVS: whereas before the onset of CVS there was no difference between patients that later developed CVS and the control group, after the onset of CVS, CrCP became significantly lower in comparison to the control group.

Because CrCP is the sum of ICP and WT[19]**,** any observed changes could be the end result of alterations in either variable. The onset of CVS did not cause any significant changes in ICP, which remained at relatively low levels. Therefore, the observed changes in CrCP could be reflecting changes in WT, where a reduced WT would be signifying a reduced vasomotor tone and dilated vessels. This preliminary inference would be in agreement with previous studies demonstrating dilated parenchymal small arteries and arterioles in the low perfusion area distal to spasm[11–14,34], attributed to a possible autoregulatory response[35,36].

The behavior of the microvasculature during CVS has previously attracted considerable interest, although both clinical and experimental studies have produced conflicting results[11–

[15]. A better understanding of microcirculatory changes may lead to better ways of maintaining adequate local perfusion pressure, which otherwise gets significantly affected by the stenosis[3–5]. Lowering of CrCP during spasm for most investigators is counterintuitive; spasm increases tension of conductive vessels, therefore CrCP should rather rise than decrease. But CrCP describes better the state of resistive arterioles rather than conductive vessels[19]. Spasm in conductive vessels decreases effective cerebral perfusion pressure at the level of the resistive arterioles, causing dilation, a decrease in wall tension, and decreases in CrCP.

Clinical significance

The changes in CrCP occurred despite the initiation of triple-H therapy, which includes raising of ABP[30]. Normally, arterial hypertension causes vasoconstriction[35,37], which is known to lead to a higher CrCP through an increased WT[26]. Therefore, the observed decreases in CrCP could signify a strong dilatatory effect of proximal vasospasm on distal microcirculation.

A lower CrCP after the onset of CVS was associated with an unfavorable outcome, in contrast to FV. As the level of FV is of high importance in TCD-assessed vasospasm[23,29,36], this preliminary finding denoting the relationship of CrCP with FV and outcome deserves further discussion. With CrCP appearing to express changes in microcirculation, this finding could enhance its clinical importance, potentially denoting its role as a quantitative surrogate marker of dilated vessels being associated with a worse outcome.

Furthermore, before the CVS onset an inverse association was found between CrCP and autoregulation: a lower CrCP being linked with a higher Sxa or worsening of autoregulation. This relationship could be explained by an apparent reduced pressure reactivity due to vessels

becoming dilated and therefore having a lower vasomotor tone, expressed with a reduced CrCP. A similar relationship between WT and autoregulation has been previously observed in traumatic brain injury[38].

Advantages of impedance-based CrCP

The main advantage of impedance CrCP is that its renderings in SAH patients agreed with the findings of an earlier study using two traditional CrCP methods[24], without presenting though any negative values for this pathology, as has been also verified with this estimation method in both experimental and clinical scenarios.[26,27,31,38].

Despite CrCP calculations being based on FV-derived information, the changes in CrCP during CVS were independent from changes in FV, therefore not being artificially driven by increasing FV[24] but rather being representative of changes in the physiology of the microvasculature. Most importantly the calculations with our method were not affected by the diameter change of the insonated vessel, as the calculation of CrCP is independent of the insonated vessel's unknown cross-sectional area (please see Appendix)[26,33].

All of the above makes the new impedance based measures of CrCP superior to the traditional methods and suitable for use in clinical practice, particularly in SAH patients where vasospasm has occurred.

Limitations

Calibration of ABP at heart-level instead of brain-level could be considered a confounding factor in this study, leading to an overestimation of ABP at the level of the insonated vessel[39], potentially affecting therefore impedance CrCP calculations. However, this study explored the changes in CrCP caused by the presence of vasospasm, rather than assessing absolute

values of CrCP. Therefore the use of this ABP calibration, consistent throughout the measurements with patients having an unchanged 30-45 degrees head up, could be considered as adequate for the purposes of this study.

In contrast to continuous ABP measurements, TCD recordings were performed for short periods (30 to 60 minutes) for every patient on a day-to-day basis[16]. This means that calculation of CrCP was only possible when the recordings of ABP and FV were combined during these short periods. This is a known limitation of the TCD methodology at present, and one that can only be overcome by the advent of new self-focusing TCD probes. Nevertheless, these 'snapshots' of CrCP were deemed adequate for the aims of the study[16].

The overall number of patients may pose a limitation for this study. However, despite the small number of patients, the results were able to: a) present an agreement with the results of a past study[24] b) demonstrate at the same instance the strength of the reliable impedance CrCP method and c) preliminary indicate an association of CrCP with a worse outcome, independently to FV, which consists of a widely used marker of CVS. Furthermore, the lack of a multivariate regression model for outcome assessment is a limitation for this study. A prospective study with a larger number of patients will be able to further explore the relationship of CrCP with outcome, through a multivariate regression analysis taking under consideration other parameters such as age, sex, WFNS score etc. With a larger sample of SAH patients a further analysis could investigate whether a specific threshold for CrCP predicting a worse outcome could be identified.

Furthermore, the small number of patients with ICP measurements for assessing changes occurred during CVS could be considered as a limitation, mainly attributed to the fact that SAH patients do not routinely receive intracranial monitoring[16]. However, similar findings

regarding the effect of CVS on ICP have been presented before, therefore confirming our results.[24]

Conclusions

The presence of vasospasm significantly reduced CrCP, as seen in temporal assessment where the onset of vasospasm resulted in a decrement of CrCP, and in spatial assessment, where vasospasm caused an interhemispheric CrCP difference, with a lower CrCP ipsilateral to spasm.

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Disclosure/Conflict of Interest

ICM+ Software is licensed by Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus/. MC and PS have a financial interest in a fraction of the licensing fee. The corresponding author and the rest of the co-authors do not have any conflict of interest.

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Titles and legends to figures

Figure 1: Dichotomization of patients into study groups, considering the aims of each comparison and the availability of monitored signals. From a cohort of 98 patients with subarachnoid hemorrhage (SAH), patients that developed cerebral vasospasm (CVS) were studied (52). From this group, the intracranial pressure (ICP) part consisted of a total of 21 patients with monitoring of ICP. Out of these 21 patients, 14 had ICP measurements both before and during CVS and were used for assessing changes in ICP following the onset of CVS. For the CrCP part, 37 patients were used for CrCP comparisons, after fulfilling the criteria of full measurements, regarding presence of arterial blood pressure (ABP) and bilateral transcranial Doppler flow velocity (FV) both before and during CVS.

Figure 2: Bilateral comparison of critical closing pressure (CrCP) for periods before and during vasospasm (CVS): CVS causes asymmetry with ipsilateral CrCP becoming significantly lower than contralateral, whereas in contrast, no significant interhemispheric difference was found before CVS. Error bars represent +/- 2 standard errors.

Figure 3: Association of critical closing pressure (CrCP) after the onset of vasospasm (CVS) with outcome of patients (N=37) at both discharge **(A)** and 3 months post subarachnoid hemorrhage (SAH) **(B)**. In both time points, unfavorable outcome cases presented a significantly lower CrCP, in comparison to favorable cases. Error bars represent +/- 2 standard errors.

Tables

Table 1 Characteristics of patients with cerebral vasospasm, consisting of a subgroup of the total cohort of patients with subarachnoid hemorrhage. Section A presents overall characteristics, with Section B comparing characteristics of patients with favorable and unfavorable outcomes.

Section	Variable		Value	
A	**Number of Patients, n**		52	
	Age, median years (IQR)		52 (45-60)	
	Sex, female/male		36/16	
	WFNS grade, median		**Modified Fisher grade, median**	
	1, n	16	**1, n**	9
	2, n	16	**2, n**	6
	3, n	2	**3, n**	29
	4, n	12	**4, n**	8
	5, n	6	-	
	Aneurysm location, n			
	ACA	2	**MCA**	11
	AChA	3	**PComA**	16
	AComA	14	**PCA**	0
	BA	1	**PICA**	1
	ICA	3	**VBJ**	0
	Clipping/coiling, n	39/17	**Re-bleeding, n**	0
	Surgical Infarcts, n	8	**Hydrocephalus, n**	28

	Outcome (N=37 patients)			
	median GOS at 3 months		5 (IQR: 4-5)	
	Favorable vs. Unfavorable			
	Parameter	**Favorable**	**Unfavorable**	**p-value**
B	**Number of patients, n**	**29**	8	-
	Age, median years (IQR)	54 (45-62)	53 (49-63)	0.732
	Sex, female/male	21/8	4/4	-
	WFNS grade, median	2	4	0.003*
	Modified Fisher grade, median	3	2	0.332
	Hydrocephalus	16	6	-
	DCI	15	6	-

Abbreviations: ACA: anterior cerebral artery; **AChA:** anterior choroidal artery; **AComA:** anterior communicating artery; **BA:** basilar artery; **ICA:** internal carotid artery; **IQR:** interquartile range; **MCA:** middle cerebral artery; **PCA:** posterior cerebral artery; **PComA:** posterior communicating artery; **PICA:** posterior inferior cerebellar artery; **VBJ:** Vertebrobasilar junction; **WFNS:** scale of World Federation of Neurosurgical Societies **GOS:** Glasgow Outcome Scale; *: significant difference – independent samples test.

Table 2 Comparison of mean values and standard deviations (mean ± SD) of parameters before and during cerebral vasospasm (Paired Samples T-test)

N=37	Before CVS	During CVS	p-value
CrCP [mm Hg]	40.70 ± 16.72	34.71 ± 9.85	P=0.025
FV [cm/s]	80.38 ± 24.21	153.41 ± 42.99	P<0.001
ABP [mm Hg]	90.33 ± 14.64	103.39 ± 18.78	P<0.001

Abbreviations: CVS, cerebral vasospasm, **CrCP,** critical closing pressure; **FV**, blood flow velocity; **ABP**, arterial blood pressure. Both CrCP and FV parameters refer to ipsilateral to CVS measurements

Table 3 Interhemispheric difference in CrCP, patient-averaged by day post-SAH from the onset of spasm and onwards (median onset for all patients: 6 days post SAH). Based on clinical assessment, the monitoring time was not equivalent for all patients, therefore the number of available patients analyzed for each day is denoted.

Days post SAH	**Number of Patients**	**ΔCrCP [mean±SD; mm Hg]**
6	median onset of spasm	
7	20	0.66±5.79
8	21	3.24±7.37
9	24	2.79±5.68
10	20	1.62±8.69
11	12	6.87±5.27
12	11	5.14±6.77
13	10	1.75±6.60

Abbreviations: CrCP, critical closing pressure; ΔCrCP, interhemispheric differences in CrCP; **SAH,** subarachnoid hemorrhage

559 **Table 4**: Binary Logistic Regression Model for predicting outcome.

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Outcome (Favorable vs Unfavorable)	Parameters	B (standard Error)	Wald	p	OR	95% CI for OR
Discharge	CrCP	0.099 (0.045)	4.82	0.028	1.105	1.011-1.207
	FV	-0.010 (0.008)	1.702	0.192	0.990	0.974-1.005
3 months	CrCP	0.104 (0.052)	3.991	0.046	1.110	1.002-1.229
	FV	-0.011 (0.009)	1.524	0.217	0.989	0.972-1.007

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562 **Abbreviations: CrCP,** critical closing pressure; **FV**, flow velocity; **OR**, odds ratio; **CI**,
563 confidence interval.

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Appendix

Calculation of non-invasive CrCP

The basis of non-invasive CrCP is a multi-parameter invasive model, derived from the concept of impedance[25,26]:

$$CrCP = ABP - \frac{CPP}{\sqrt{(CVRi \cdot Ca \cdot HR \cdot 2\pi)^2 + 1}} \qquad \textbf{(1)}$$

The invasive parts requiring ICP measurements are CPP (calculated as ABP-ICP) and cerebrovascular resistance (CVRi), approximated as[40]:

$$CVRi = \frac{CPP}{FV \cdot S_a} \quad [\frac{mm\ Hg \cdot s}{cm^3}]$$

The parameter S_a in the denominator represents the unknown cross-sectional area of the insonated vessel.

Ca can be estimated as[32,33]:

$$Ca = \frac{CaBV1 \cdot Sa}{A1} \quad [\frac{cm^3}{mm\ Hg}]$$

A1: fundamental harmonic amplitude of ABP; CaBV1: amplitude of the fundamental harmonic of cerebral arterial blood volume (CaBV), derived by using a 10-second discrete Fourier transformation of CaBV's time series. CaBV is approximated by integrating FV pulse waveform with the beat-to-beat mean removed[32,33].

The product of Ca and CVRi in eq. (1) cancels out the parameter S_a, as has been described in the impedance methodology[26].

Approximating CrCP non-invasively, we used the CrCP formula, substituting CPP with ABP, with CVRi being now approximated non-invasively as[40]:

$$CVR = \frac{ABP}{FV \cdot S_a} \quad [\frac{mm\ Hg \cdot s}{cm^3}]$$

With these substitutions, the non-invasive model of impedance CrCP is now rendered as[31]:

$$CrCP = ABP \cdot [1 - \frac{1}{\sqrt{(CVR \cdot Ca \cdot HR \cdot 2\pi)^2 + 1}}] \qquad \textbf{(2)}$$